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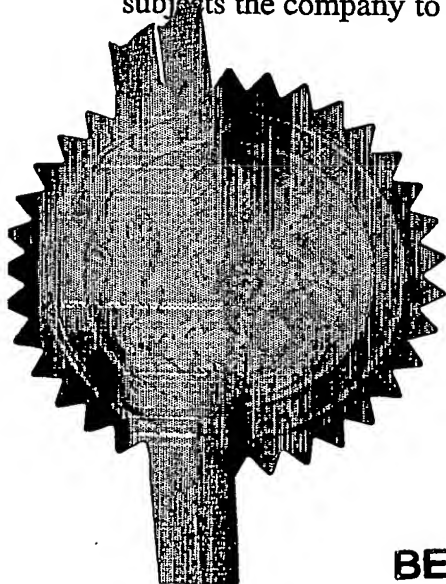
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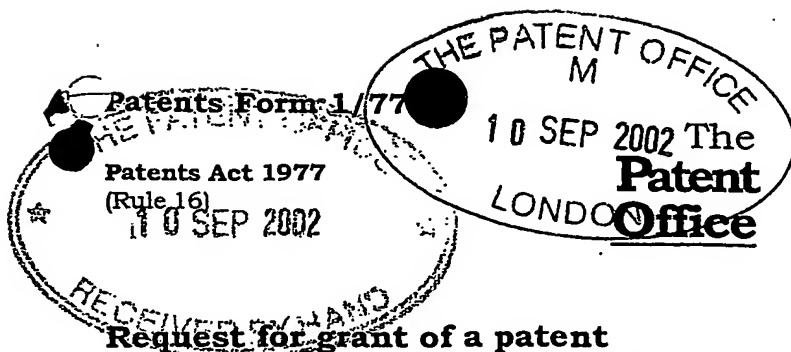
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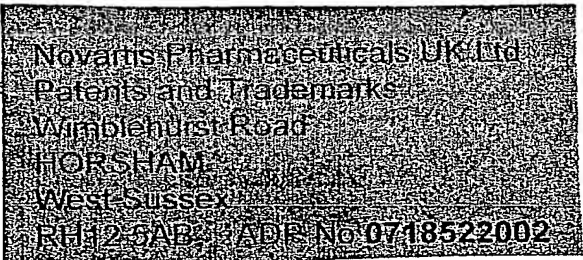
1/77

Request for grant of a patent

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1.	Your reference	4-32655P1		
2.	Patent application number (The Patent Office will fill in this part)	10 SEP 2002		0220953.4
3.	Full name, address and postcode of the or of each applicant (underline all surnames)	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND 0712 5487 005 Patent ADP number (if you know it) If the applicant is a corporate body, give the country/state of its incorporation		
4.	Title of invention	Organic compounds		
5.	Name of your agent (If you have one) "Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode) Patents ADP number (if you know it)			
6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority application number (if you know it)	Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)	
8.	is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if: a) any applicant named in part 3 is not an inventor, or b) there is an inventor who is not named as an applicant, or c) any named applicant is a corporate body. (see note (d))	Yes		

Patents Form 1/77

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Continuation sheets of this form

Description 10 ✓

Claim(s) 2 ✓

Abstract 1 ✓

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Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*) ONE ✓

Request for substantive examination (*Patents Form 10/77*)

Any other documents
(please specify)

11. I/We request the grant of a patent on the basis of this application

Signature

Date

B.A. Yorke & Co.

B.A. Yorke & Co.

10 September 2002

12. Name and daytime telephone number of person to contact in the United Kingdom
Mrs. E. Cheetham
020 8560 5847

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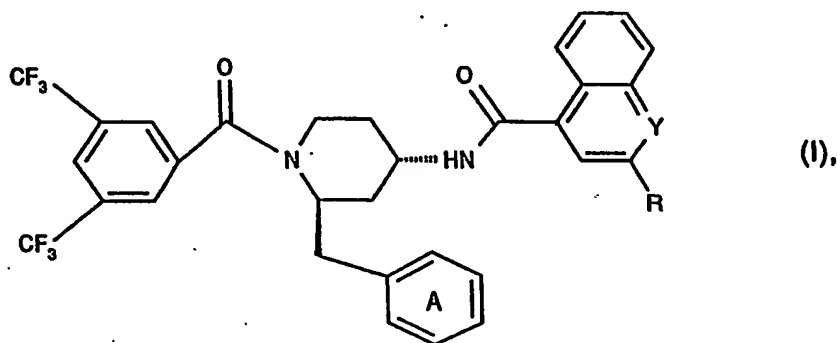
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Organic Compounds

The invention relates to novel N-(3,5-bis-trifluoromethyl-benzoyl)-2-benzyl-4-(quinoloyl-amino)-piperidines of the formula



wherein Y is =N- or =N(O)-, R is OH when Y is =N- and R is H when Y is =N(O)- and the ring A is unsubstituted or mono- or poly-substituted by substituents selected from the group consisting of lower alkyl, lower alkoxy, halogen, nitro and trifluoromethyl, provided that when R is OH and Y is =N- the ring A is not unsubstituted; to the use thereof; to processes for the preparation thereof and to pharmaceutical compositions comprising a compound according to the invention.

Since the compounds according to the invention have at least two optically active carbon atoms they may accordingly be present in the form of stereoisomers, stereoisomeric mixtures and in the form of the (substantially) pure diastereoisomers. The present invention relates also to corresponding stereoisomers.

Preference is given to compounds of formula I wherein the ring A is substituted.

Unless otherwise defined, the general terms used hereinbefore and hereinafter have the meanings given below.

The term "lower" denotes that groups and compounds so defined each have from 1 up to and including 7, preferably from 1 up to and including 4, carbon atoms.

Lower alkyl is, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl or a corresponding pentyl, hexyl or heptyl radical. C₁-C₄alkyl is preferred.

Lower alkoxy is, for example, methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy, isobutyloxy, sec-butyloxy, tert-butyloxy or a corresponding pentyloxy, hexyloxy or heptyloxy radical C₁-C₄alkoxy is preferred.

Halogen is especially halogen having an atomic number of up to and including 35, i.e. fluorine, chlorine or bromine, and also includes iodine. Chlorine is preferred.

Substance P is a naturally occurring undecapeptide of the tachykinin family. It is produced in mammals and acts pharmacologically as a neuropeptide. Substance P plays an important role in various disorders, for example in the case of painful conditions, in migraines and in certain disorders of the central nervous system, such as anxiety states, vomiting, schizophrenia and depression, and in certain motor disorders, such as Parkinson's disease, but also in inflammatory diseases, such as rheumatoid arthritis iritis and conjunctivitis, in diseases of the respiratory organs, such as asthma and chronic bronchitis, in diseases of the gastrointestinal system, such as ulcerative colitis and Crohn's disease, and in hypertension.

A great deal of work is being done to advance the development of the field of substance-P-antagonists and, for example, to find suitable substance-P-antagonists having a broad spectrum of action that exhibit outstanding *in vivo* activity and increased bioavailability as well as improved chemical stability.

Extensive pharmacological studies have shown that the compounds according to the invention antagonise substance P to an especially preferred extent and thus inhibit the symptoms induced by substance P.

The substance-P-antagonising effects can be demonstrated - as shown below - using test methods known to the person skilled in the art. Such effects are observed both *in vitro* and *in vivo*. For example, the substance-P-induced formation of phosphoinositol in human astrocytoma cells is antagonised *in vitro* by the compounds of formula I and IA. IC₅₀ values of from approximately 1 nmol are found. A suitable test model for the detection of that

inhibition is, for example, the test method of Lee, C.M. *et al.*, as described in *J.Neurochem.* 59, 406-414 (1992).

In addition, the binding of ^3H -substance P to bovine retina in the radio receptor assay according to H. Bittiger, Ciba Foundation Symposium 91, 196-199 (1982) is inhibited with IC_{50} values of from approximately 1 nmol. For example, the following *in vitro* values of about 10 nM were obtained for the target compounds of Examples 1 and 2.

A change in behaviour is produced in gerbils by i.c.v. administration of substance P methyl ester. That effect can be inhibited *in vivo* after peroral administration of compounds of formulae I and IA and the salts thereof. A.Vassout *et al.* which was presented at the "Substance P and Related Peptides: Cellular and Molecular Physiology" Congress in Worchester, Mass., in 1990. In that method, ED_{50} values of from approximately 0.1 mg/kg p.o. are obtained, demonstrating their usefulness in the treatment of disorders of the central nervous system.

In vivo, using the experimental procedure of Lundberg *et al.*, Proc. Nat. Acad. Sci. (USA) 80, 1120-1124, the compounds of formulae I and IA and the salts thereof inhibit vagally induced bronchospasms in guinea pigs at a dose of from approximately 1.0 mg/kg i.v., which demonstrates their suitability for the treatment of asthma.

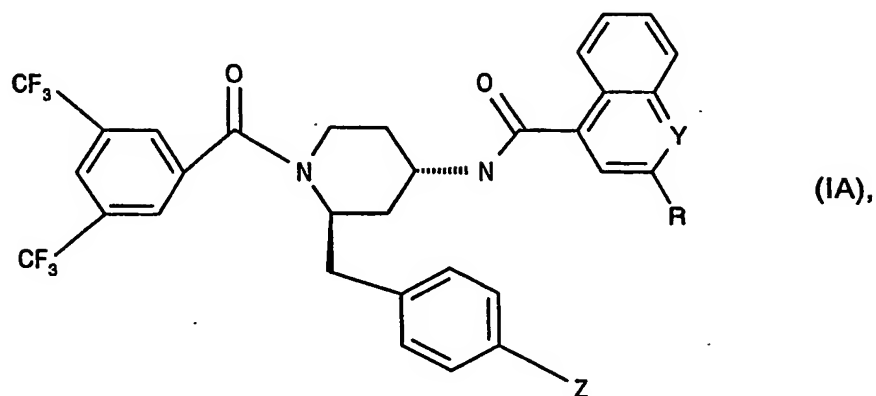
The substance-P-antagonists of formulae I and IA prepared in accordance with the invention and the pharmaceutically acceptable salts thereof are accordingly outstandingly suitable for the therapeutic treatment of the pathological symptoms listed hereinbefore.

The invention relates also to a method of treating disorders induced by substance P by the administration of a therapeutically effective amount of a compound of formula I or IA.

The present invention relates also to the use of a compound of formula I or IA in the preparation of medicaments for the treatment of disorders induced by substance P.

The invention relates also to the use of compounds of formula I or IA as biochemical tools, for example for the identification and, possibly, the profiling of further potent substance-P-antagonists.

The invention relates especially to compounds of formula IA

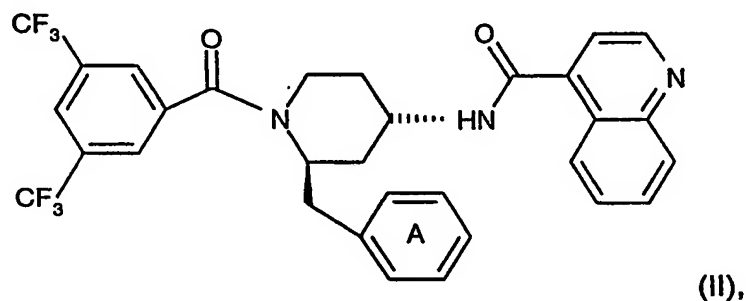


wherein Y and R are as defined above and Z is hydrogen, halogen or nitro, provided that when R is OH and Y is =N- Z is not H.

The invention relates above all to compounds of formula IA wherein Y and R are defined above and Z is halogen, such as chlorine.

The invention relates specifically to the compounds of formula I mentioned in the Examples.

The invention relates also to processes for the preparation of the compounds according to the invention. Those processes comprise oxidising a compound of formula II



and, if desired, separating a mixture of isomers obtainable by the process and isolating the desired isomer.

The compound of formula II may be oxidised to give a compound of formula I; for instance, with 3-chloroperbenzoic acid at room temperature.

Alternatively compounds of formula I in which R is OH and Y is =N- may be prepared by linking of the corresponding [(2R, 4S)-4-Amino-2-(4-benzyl-piperidin-1-yl)-(3,5-bis trifluormethyl-phenyl)-methanone with 2-hydroxyquinoline-4-carboxylic acid; for instance as hereinafter described in Example 2.

The invention is illustrated especially by the Examples and relates also to the novel compounds mentioned in the Examples and to the processes for the preparation thereof.

The compounds of formula I and IA, may also be obtained in the form of hydrates or may include the solvent used for crystallisation.

Resulting mixtures of diastereoisomers and mixtures of racemates can be separated in known manner into the pure diastereoisomers or racemates on the basis of the physico-chemical differences between the constituents, for example by chromatography and/or fractional crystallisation.

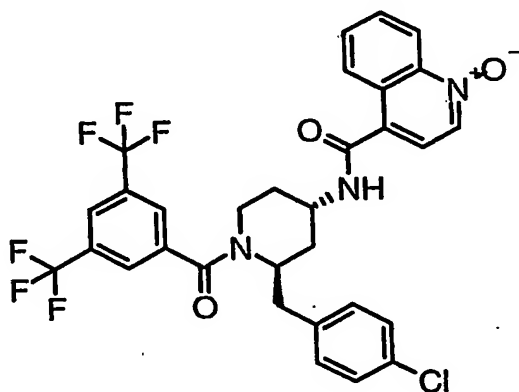
Resulting racemates can also be separated into the optical antipodes by known methods, for example by recrystallisation from an optically active solvent, with the aid of microorganisms or by reaction of the resulting diastereoisomeric mixture or racemate with an optically active auxiliary compound, for example according to the acidic, basic or functionally modifiable groups present in compounds of formulae I and IA with an optically active acid, base or an optically active alcohol, into mixtures of diastereoisomeric salts or functional derivatives, such as esters, and separation thereof into the diastereoisomers from which the desired enantiomer can be freed in the appropriate customary manner. Examples of suitable bases, acids and alcohols are optically active alkaloid bases, such as strychnine, cinchonine or brucine, or D- or L-(1-phenyl)ethylamine, 3-pipecoline, ephedrine, amphetamine and similar synthetically obtainable bases, optically active carboxylic or sulfonic acids, such as quinic acid or D- or L-tartaric acid, D- or L-di-o-toluytartaric acid, D- or L-malic acid, D- or L-mandelic acid, or D- or L-camphorsulfonic acid, or optically active alcohols, such as borneol or D- or L-(1-phenyl)ethanol.

The novel compounds of formulae I and IA can be used, for example, in the form of pharmaceutical compositions that comprise a therapeutically effective amount of the active ingredient, optionally together with inorganic or organic, solid or liquid, pharmaceutically acceptable carriers that are suitable for enteral, for example oral, or parenteral administration. There are used, for example, tablets or gelatin capsules that comprise the active ingredient together with diluents, for example lactose, dextrose, saccharose, mannitol, sorbitol, cellulose and/or lubricants, for example silica, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Tablets can also comprise binders, for example magnesium aluminium silicate, starches, such as corn, wheat, rice or arrowroot starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and, if desired, disintegrators, for example starches, agar, alginic acid or a salt thereof, for example sodium alginate, and/or effervescent mixtures, or absorbents, colourings, flavourings and sweeteners. The novel compounds of formulae I and IA can also be used in the form of parenterally administrable compositions or in the form of infusion solutions. Such solutions are preferably isotonic aqueous solutions or suspensions which, for example in the case of lyophilised compositions that comprise the active ingredient on its own or together with a carrier, for example mannitol, can be prepared before use. The pharmaceutical compositions may be sterilised and/or may comprise excipients, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers. The pharmaceutical compositions in question, which, if desired, may comprise further pharmacologically active substances, are prepared in a manner known *per se*, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes, and comprise from approximately 0.1 % to 100 %, especially from approximately 1 % to approximately 50 %, in the case of lyophilisates up to approximately 100 %, active ingredient.

The invention relates also to the use of the compounds of formulae I and IA, preferably in the form of pharmaceutical compositions. The dose can depend on various factors, such as the mode of administration, species, age and/or individual condition. The daily doses to be administered are, in the case of oral administration, from approximately 0.25 to approximately 10 mg/kg, and in the case of warm-blooded animals having a body weight of approximately 70 kg, they are preferably from approximately 20 mg to approximately 500 mg.

The following Examples illustrate the invention; temperatures are given in degrees Celsius and pressures in mbar.

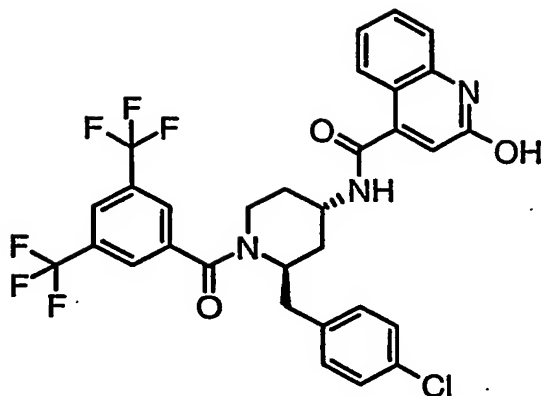
Example 1: 1-Oxy-quinoline-4-carboxylic acid [(2R,4S)-1-(3,5-bis-trifluoromethyl-benzoyl)-2-(4-chloro-benzyl)-piperidin-4-yl]-amide



To a solution of 6.0 g (9.68 mMol) quinoline-4-carboxylic acid [(2R,4S)-1-(3,5-bis-trifluoromethyl-benzoyl)-2-(4-chloro-benzyl)-piperidin-4-yl]-amide (Synthesis described in EP 707 006 A) in 60 ml of CH₂Cl₂ were added 2.07 g (10.2 mMol) of 3-chloroperbenzoic acid (85%) at room temperature with stirring. After the mixture became homogeneous it was left at room temperature for 18 hrs. The mixture was washed successively with 5% aqueous NaHSO₃ and 10% aqueous NaHCO₃. The organic phase was dried with K₂CO₃ and concentrated in vacuo. The crude product was recrystallized from MeOH/H₂O. Yield 4.9 g white crystals. Mp. 223-225°C

MS(ES⁺): [M+1]⁺= 636 and [M+23]⁺= 658.

Example 2: 2-Hydroxy-quinoline-4-carboxylic acid [(2R,4S)-1-(3,5-bis-trifluoromethyl-benzoyl)-2-(4-chloro-benzyl)-piperidin-4-yl]-amide



To a stirred mixture of 2.52 g (13.32 mMol) 2-hydroxyquinoline-4-carboxylic acid, 2.7 g (15.98 mMol) HOBt (80%), 3.7 ml (26.64 mMol) triethylamine and 3.8 g (18.64 mMol) DCC in 50 ml of CH₂Cl₂ were added at room temperature 12.3 g (13.32 mMol) [(2R,4S)-4-Amino-2-(4-chloro-benzyl)-piperidin-1-yl]-(3,5-bis-trifluoromethyl-phenyl)-methanone (synthesis described in EP 707006A). After 18 h the reaction mixture was diluted with 500 ml THF and filtered through a fritted glass funnel with suction. The filtrate was further diluted with ethyl acetate and washed three times with brine. The organic phase was dried with Na₂SO₄ and concentrated in vacuo. The product was purified by chromatography on silica gel using successively EtOAc/ CH₂Cl₂ (2:1), EtOAc and EtOAc/THF (3:1) as eluents. The product was suspended in hexane and stirred at 60°C overnight. The mixture was filtered and dried and a yield of 6.2 g of white crystals. M.p.222-224°C.

[M+1]⁺= 636 and [M+23]⁺= 658

Example 3: Tablets, each comprising 50 mg of (2R,4S)-N-[1-(3,5-bis-trifluoromethyl-benzoyl)-2-benzyl-piperidin-4-yl]quinoline-N-oxide-4-carboxamide can be prepared as follows:

Composition (10 000 tablets)

active ingredient	500.0 g
lactose	500.0 g
potato starch	352.0 g
gelatin	8.0 g
talc	60.0 g
magnesium stearate	10.0 g

silicon dioxide (highly dispersed)	20.0 g
ethanol	q.s.

The active ingredient is mixed with the lactose and 292 g of potato starch and the mixture is moistened with an ethanolic solution of the gelatin and granulated through a sieve. After drying, the remainder of the potato starch, the magnesium stearate, the talc and the silicon dioxide are mixed in and the mixture is compressed to form tablets, each weighing 145.0 mg and comprising 50.0 mg of active ingredient; the tablets may, if desired, be provided with breaking notches for finer adaptation of the dose.

Example 4: Film-coated tablets, each comprising 100 mg of (2R,4S)-N-[1-(3,5-bis-trifluoromethyl-benzoyl)-2-benzyl-piperidin-4-yl]-3-hydroxy-quinoline-4-carboxamide can be prepared as follows:

Composition (for 1000 film-coated tablets)

active ingredient	100.0 g
lactose	100.0 g
corn starch	70.0 g
talc	8.5 g
calcium stearate	1.5 g
hydroxypropylmethylcellulose	2.36 g
shellac	0.64 g
water	q.s.
methylene chloride	q.s.

The active ingredient, the lactose and 40 g of the corn starch are mixed and moistened with a paste prepared from 15 g of corn starch and water (with heating) and granulated. The granules are dried, the remainder of the corn starch, the talcum and the calcium stearate are added and mixed with the granules. The mixture is compressed to form tablets (weight: 280 mg) which are then film-coated with a solution of the hydroxypropylmethylcellulose and the shellac in methylene chloride; final weight of the film-coated tablet: 283 mg.

Example 5: Hard gelatin capsules, comprising 100 mg of active ingredient, for example (2R,4S)-N-[1-(3,5-bis-trifluoromethyl-benzoyl)-2-benzyl-piperidin-4-yl]-quinoline-N-oxide-4-carboxamide or a salt, for example the hydrochloride, thereof, can be prepared, for example, as follows:

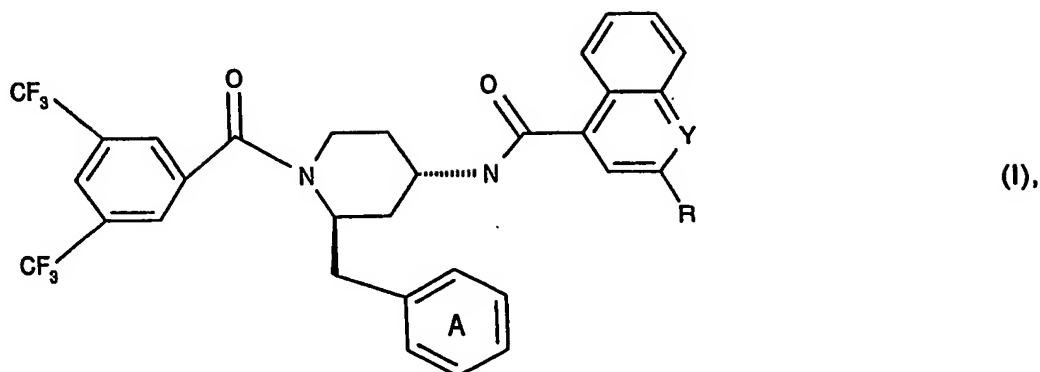
Composition (for 1000 capsules)

active ingredient	100.0 g
lactose	250.0 g
microcrystalline cellulose	30.0 g
sodium lauryl sulfate	2.0 g
magnesium stearate	8.0 g

The sodium lauryl sulfate is added to the lyophilised active ingredient through a sieve of 0.2 mm mesh size. The two components are intimately mixed. Then first the lactose is added through a sieve of 0.6 mm mesh size and then the microcrystalline cellulose is added through a sieve of 0.9 mm mesh size. The mixture is then intimately mixed again for 10 minutes. Finally the magnesium stearate is added through a sieve of 0.8 mm mesh size. After mixing for a further 3 minutes, size 0 hard gelatin capsules are each filled with 390 mg of the resulting formulation.

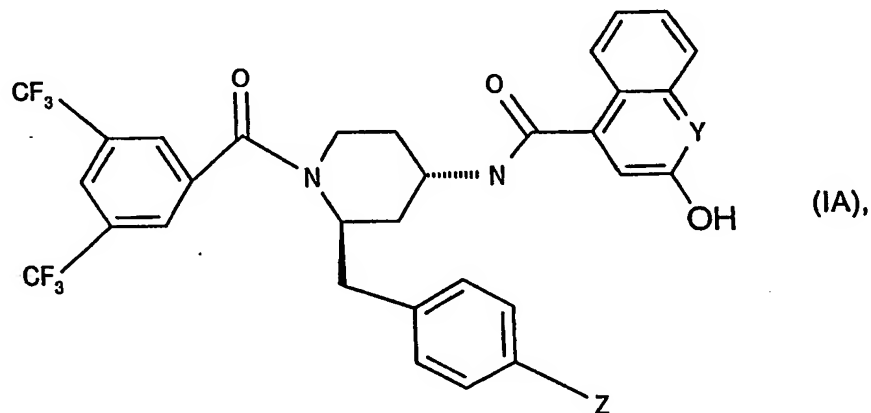
CLAIMS:

1. A compound of the formula



wherein Y is =N- or =N(O)-, R is OH when Y is =N- and R is H when Y is =N(O)- and the ring A is unsubstituted or mono- or poly-substituted by substituents selected from the group consisting of lower alkyl, lower alkoxy, halogen, nitro and trifluoromethyl, provided that when R is OH and Y is =N- the ring A is not unsubstituted.

2. A compound according to claim 1 of formula IA



wherein Y is =N- or =N(O)-, R is OH when Y is =N- and R is H when Y is =N(O)-, and Z is hydrogen, halogen or nitro, provided that when R is OH and Y is =N- Z is not H.

3. A compound according to claim 2 of formula IA, wherein Y is =N- or =N(O)-, R is OH when Y is =N- and R is H when Y is =N(O)-, and Z is halogen.

4. A compound selected from:

(2R,4S)-N-[1-(3,5-bis-trifluoromethyl-benzoyl)-2-benzyl-piperidin-4-yl]-quinoline-N-oxide-4-carboxamide or a salt thereof, and

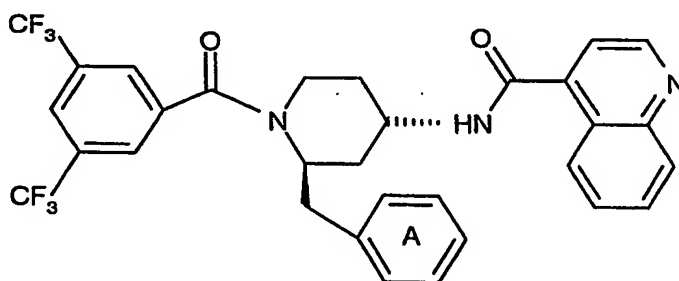
(2R,4S)-N-[1-(3,5-bis-trifluoromethyl-benzoyl)-2-benzyl-piperidin-4-yl]-3-hydroxy-quinoline-4-carboxamide.

5. A compound according to any one of claims 1 to 4 for use in a method for the treatment of the human or animal body.

6. A pharmaceutical composition comprising a compound according to any one of claims 1 to 4.

7. The use of a compound according to any one of claims 1 to 4 in the preparation of a pharmaceutical composition for the treatment of disorders induced by substance P.

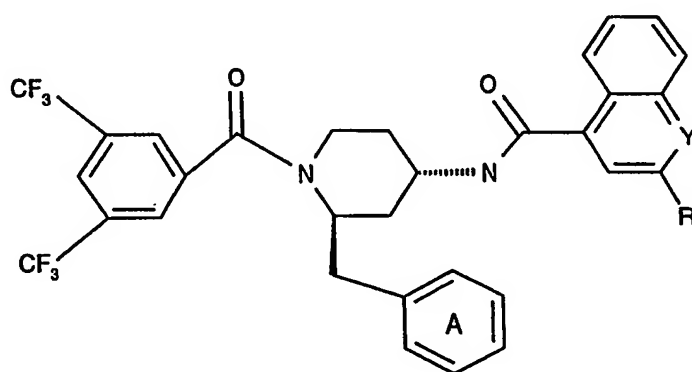
8. A process for the preparation of a compound according to any one of claims 1 to 4, which comprises oxidising a compound of formula II



and if desired, (separating a mixture of isomers obtainable by the process and isolating the desired isomer

ABSTRACT

The invention relates to novel N-(3,5-bis-trifluoromethyl-benzoyl)-2-benzyl-4-(quinoloyl-amino)-piperidines of the formula



wherein Y and R each are as defined above and the ring A is unsubstituted or mono- or poly-substituted by substituents selected from the group consisting of lower alkyl, lower alkoxy, halogen, nitro and trifluoromethyl; and the salts thereof, to the use thereof, to processes for the preparation thereof and to pharmaceutical compositions comprising a compound according to the invention.

PCT Application
EP0310007



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